

REMARKS

Claims 21, 23-29, 31, 41, and 46-57 are pending in this application. Claims 21, 23-29, 31, 41, and 46-57 were variously rejected under 35 U.S.C. §103.

By this amendment, claims 21 and 41 have been amended without prejudice or disclaimer of any previously claimed subject matter. Applicants respectfully request entry of the amendment.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §103

Claims 21, 23-29, 31, 41, and 46-57 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over Madden (U.S. Pat. No. 5,389,378) or Liu (U.S. Pat. No. 5,707,608) or Desai et al. (U.S. Pat. No. 6,074,666, "Desai"). Claims 21, 23-29, 31, 41, and 46-57 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over Madden or Liu or Desai in view of either Lentini (U.S. Pat. No. 5,885,557) or Young (U.S. Pat. No. 6,375,930) in further combination with Wan (U.S. Pat. No. 5,329,029). Applicants respectfully traverse these rejections.

The claimed invention is directed to a micelle composition in which the micelles in the composition have an average diameter below about 100 nm. The claimed micelles comprise

saturated and unsaturated phospholipids and one or more hydro-monobenzo-porphyrin photosensitizer.

Claims 21, 23-29, 31, 41, and 46-57 over Madden or Lui or Desai

Madden, Lui and Desai describe liposomal compositions and, as the Examiner admits, Madden, Lui and Desai all lack explicit teachings of micelle compositions. The Examiner states, however, that Madden, Lui and Desai “teach high energy processing steps” and that it would be obvious to the skilled artisan that the compositions in the references “would also contain micelles besides liposomes.” The Examiner appears to be confusing obviousness with inherent anticipation in this rejection. Applicants respectfully disagree with both this characterization of the teachings of cited references and with the assertions of obviousness regarding the claimed invention.

Since inherency is being relied upon for this rejection, “the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.” *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI, 1990) (emphasis in original). “To establish inherency, the extrinsic evidence ‘must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.’” *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); M.P.E.P. §2112.

Since the Office is saying that these compositions inherently include micelles as claimed, it must show that this is indeed the case. This showing, however, has not been provided nor has the Office provided basis that this position supports the obviousness rejection. If the Examiner feels

that the invention is inherently anticipated, the rejection should be characterized as such and proper basis must be provided to establish inherent anticipation.

The Examiner also asserts that “if formation of micelles were preferred, it would have been obvious to subject the phospholipid preparations to high energy processing steps till the formulations contain only micelles of desired sizes.” Office Action, page 3. However, this statement does not support an obviousness rejection. To support this rejection, the Office must show why an artisan would prefer micelles. Not only do none of the references show that micelles as claimed are produced by the process methods used, none of the cited references suggest that micelles as claimed should be prepared.

Madden does not teach or suggest the use of a high energy process for the preparation of liposomes but rather teaches use of an extrusion process to generate appropriate sized liposomes “ranging from about 100 to about 120 nm in diameter.” See, for example, col. 6, lines 36-59, and col. 12, lines 27-60. As noted in the specification, the extrusion process does not produce micelles of the present invention. Further, Madden does not provide any motivation or suggestion for the modification of the teachings therein to generate a micelle composition with an average diameter below about 100 nm. As such, Madden does not provide to one skilled in the art any expectation of success with regard to the claimed micelle composition having an average diameter below about 100 nm.

Although Lui mentions the use of high energy processes for the preparation of liposomes, Lui describes only the production of liposomes and, in the Example section, reports only the production of liposomes larger than 150 nm in diameter. For example, the preparation process taught in Example 5 resulted in liposome particles which averaged in size between 150 and 300 nm (col. 19, lines 5-32). In fact, when microfluidization steps are used, Lui cautions that as the number

of microfluidization passes is increased, “more of the hydrophobic hydro-monobenzoporphyrin photosensitizer molecules are squeezed out of the liposomes, increasing the tendency of the liposomes to aggregate into larger particles.” Lui, col. 12, lines 7-11. In addition, Liu describes that hydro-monobenzo-porphyrin are not soluble in micellar solutions and states that such photosensitizers may be administered by using a liposome composition (col. 7, lines 32-42). Accordingly, Lui teaches away from the claimed invention. Thus, taken in its entirety, Lui does not provide any motivation or suggestion for the modification of the teachings therein to generate a micelle composition with an average diameter below about 100 nm. Further, Lui does not provide one skilled in the art any expectation of success with regard to the claimed composition.

Desai does not teach or suggest use of a high energy processing step for the preparation of liposomes. As shown in Table I, the liposome preparation process of Desai generates liposomes with mean particle size greater than 100 nm (132-189 nm). Thus, Desai does not teach or suggest micelle compositions as claimed nor a process required for the formation of micelles as taught in the present invention. Desai states that the liposomal formulation taught therein “provides liposomes of sufficiently small and narrow particle size such that is can be manufactured without filtering to separate off larger particles or utilizing other mechanical methods of obtaining a narrow distribution of particle size.” Desai, col. 6, line 65, to col. 7, line 2, emphasis added. Thus, Desai provides no motivation or suggestion for the modification of the teachings therein to incorporate a high energy processing step for the generation of a micelle composition with an average diameter below about 100 nm. Desai also does not provide one skilled in the art any expectation of success with regard to the claimed composition given both the lack of teaching and lack of suggestion to modify the process taught in Desai.

Applicants respectfully submit that basis has not been provided to show that the claimed composition with micelles having an average diameter below about 100 nm necessarily flows from the teachings of Madden or Lui or Desai.

The Examiner was not persuaded by previous arguments regarding these references and states that Applicants “are using art known liposome method of preparation steps such as aseptic filtration of the composition through 0.22 micron filters or micro fluidizers, sonicators, high-shear mixers and homogenizers (pages 35, 38, 43 and 45) which are the same as the methods employed by Madden, Lui and Desai.” Office Action, page 6. The claimed invention is directed to a micelle composition with the micelles having an average diameter below about 100 nm but the instant specification teaches methods for the preparation of both liposome and micelle compositions. Applicants respectfully submit that the fact that the specification teaches methods for the preparation of microparticles having an average diameter larger than 100 nm has no bearing on the Examiner’s *prima facie* case of obviousness in view of the cited references.

Applicants respectfully submit that a *prima facie* case of obviousness has not been made. Thus, Applicants respectfully submit that the claimed invention is not obvious in view of Madden or Lui or Desai.

Claims 21, 23-29, 31, 41, and 46-57 over Madden or Lui or Desai in view of Lentini in further combination with Wan

A *prima facie* case of obviousness requires that three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The

teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established. As presented below, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

As discussed above, the primary references of Madden or Lui or Desai do not teach or suggest micelle compositions as claimed and do not support a *prima facie* case of obviousness over the claimed invention.

Lentini mentions micelles along with liposomes and gels as formulations for use in sustained-release delivery of psoralen. However, Lentini does not teach or suggest micelle compositions with micelles having an average diameter below about 100 nm as claimed nor methods to produce micelle compositions as claimed. Wan makes the general statement that phospholipids are capable of forming micelles and bilayers in an aqueous medium at column 2, lines 3-5, but does not provide any teaching as to methods and conditions necessary for the production of micelles nor with regard to micelles having an average diameter below about 100 nm.

Thus, Lentini in combination with Wan do not supply what is missing from the primary reference, Madden, Liu or Desai. The combinations of Madden or Liu or Desai and the secondary references do not provide any suggestion or motivation to modify the teachings therein to arrive at the claimed invention and, thus, do not render the claimed invention obvious. In addition, since none of these references, alone or in combined, teaches or suggests methods to produce micelles comprising saturated and unsaturated phospholipids and one of more hydro-monobenzo-porphyrin photosensitizer in which the micelles have an average diameter below about 100 nm, the references

do not provide a reasonable expectation of success of the claimed invention. Thus, a *prima facie* case of obviousness has not been established for the cited references.

Claims 21, 23-29, 31, 41, and 46-57 over Madden or Lui or Desai in view of Young in further combination with Wan

As discussed above, the primary references of Madden or Lui or Desai do not teach or suggest micelle compositions as claimed and do not support a *prima facie* case of obviousness over the claimed invention. Wan makes the general statement that phospholipids are capable of forming micelles and bilayers in an aqueous medium but does not provide any teaching as to methods and conditions necessary for the production of micelles generally nor for the production of micelles of having an average diameter below about 100 nm.

Young describes micelles containing texaphyrin-lipophilic molecule conjugates but is silent with regard to formation of micelles that contain hydro-monobenzo-porphyrin photosensitizer as claimed. Although texaphyrin and hydro-monobenzo-porphyrin are both photosensitive compounds, the texaphyrin-lipophilic molecule conjugate of Young and the claimed hydro-monobenzo-porphyrin are different, distinct compounds. The Examiner states that “it is unclear whether [Young] specifically advocates [phospholipid] use in the micelle formation” but goes on to assert that the combination of Young, Wan and the primary references makes obvious the claimed invention. Office Action, page 5. Applicants respectfully disagree with this assertion.

Applicants respectfully point out that the reasonable expectation of success for *prima facie* obviousness must be found in the prior art. The Examiner states that “Young shows the ability of phospholipid micelles to encapsulate active agents and this ability of micelles to encapsulate any agent will be the same and applicant has not shown that to be otherwise.” Office Action, page 7, emphasis added. Notably, Young teaches that conjugation of the lipophilic molecule to the

texaphyrin is an important aspect for vesicle loading success of the compound and that attempted loading with the texaphyrin alone was not successful. Young, col. 10, lines 33-36. Thus, contrary to the Examiner's assertion, Young indicates that active agent encapsulation is not necessarily the same of any agent. Thus, the teaching of Young does not provide an expectation of success for the claimed invention. Further, this teaching of Young together with Lui's discussion that hydro-monobenzo-porphyrin are not soluble in micellar solutions combines to move the skilled artisan even further from an expectation of success.

Thus, Applicants submit that Young and Wan do not supply what is missing from the primary reference, Madden, Liu or Desai. The combinations of Madden or Liu or Desai and the secondary references do not provide any suggestion or motivation to modify the teachings therein to arrive at the claimed invention and, thus, do not render the claimed invention obvious. In addition, since none of these references, alone or in combination, teaches or suggests methods to produce micelles comprising saturated and unsaturated phospholipids and one of more hydro-monobenzo-porphyrin photosensitizer in which the micelles have an average diameter below about 100 nm, the references do not provide a reasonable expectation of success of the claimed invention. Thus, a *prima facie* case of obviousness has not been established for the cited references.

In sum, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Applicants believe that all issues raised in the Office action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 273012011300.

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